REMARKS

The Official Action dated June 15, 2004 has been carefully considered. Additionally, the telephone interview which Examiner Berko and Examiner Spear courteously afforded Applicants' representative on October 29, 2004 is acknowledged and appreciated. The substance of the interview is discussed in detail below. Accordingly, it is believed that the present application is now in condition for allowance. Reconsideration is respectfully requested.

More particularly, during the telephone interview, the undersigned discussed with the Examiners the showings set forth in the first Declaration Under 37 C.F.R. 1.132 filed August 21, 2002 and the showings set forth in the second Declaration Under 37 C.F.R. 1.132 filed December 4, 2003. As discussed, the first Declaration demonstrates that hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), and ethylcellulose (EC) exhibit significantly different dissolution properties as demonstrated in Table 2 at page 2 of the first Declaration. As further discussed, the second Declaration shows that compositions containing a model drug and HPMC in combination with HEC exhibit significantly different dissolution properties as compared with compositions containing a model drug and HPMC, and with compositions containing a model drug and HEC, as set forth in paragraph 4 at page 2 of the second Declaration. The Examiners agreed that the showing set forth in the second Declaration rebutted any prima facie case of obviousness based on Sangekar et al, Stupak et al and Zhang et al, the references employed in the most recent Official Action. Finally, the Examiners asserted that as the present application only discloses the use of ethylcellulose as the first intelligent polymer, the claim should recite that the first intelligent polymer comprises ethylcellulose.

Accordingly, by the present amendment, claims 1, 30 and 33 are amended to more specifically recite that the first intelligent polymer comprises ethylcellulose, as previously set forth, for example, in claims 14, 19, 23 and 34. Claims 7 and 30 are amended to correct typographical errors. It is believed that these changes do not involve any introduction of new matter, and do not raise any new issues subsequent to final rejection, whereby entry of the amendments is believed to be in order and is respectfully requested.

In the Official Action, claims 1-3 and 5-34 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Sangekar et al U.S. Patent No. 5,000,962 in view of the Stupak et al U.S. Patent No. 5,162,117 and the Zhang et al U.S. Patent No. 6,083,532. The Examiner asserted that the scope of the differential release rates of drug incorporated within polymers presented in the Declarations is different from the scope of claims 1-3 and 5-22 and that the remaining claims 23-34 are directed toward process claims falling outside of the scope of the Declarations. The Examiner concluded that Stupak et al disclose controlled release of flutamide and the combination of the disclosures of the cited prior art permits one of ordinary skill in the art to design an experiment to obtain a biphasic controlled release of drug and thereby expect the results presented in the Declarations.

Initially, Applicants note that claims 1-3 and 5-35 are pending. Moreover, as discussed with the Examiners during the aforementioned interview, the controlled release pharmaceutical compositions and processes for manufacture of such compositions as defined by independent claims 1, 14, 19, 23, 30, 33 and 34, and the claims dependent thereon, are nonobvious over and patentably distinguishable from the combination of Sangekar et al with Zhang et al and Stupak et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

The controlled release pharmaceutical compositions defined by claims 1, 14, 19, 30, 33 and 34 each require ethylcellulose as a first polymer component and, importantly, the combination of hydroxyethylcellulose (HEC) and hydroxypropylmethylcellulose (HPMC) as a second polymer component. Similarly, the process for the manufacture of a sustained release composition of pharmaceutically active substance defined by claim 23 employs the combination of HEC and HPMC, and further specifies the addition of ethyl cellulose (EC). As discussed with the Examiner during the interview, Applicants have discovered that a controlled release pharmaceutical composition with the claimed combination of HEC and HPMC provides both good immediate dosing of an active and good delayed dosing of the active. Such controlled release pharmaceutical properties are desirable with many actives, particularly high potency actives where immediate dosing of some, but not all, of the active is desired.

Sangekar et al disclose a long acting diltiazem formulation containing swellable hydrophilic polymers. Examples of the swellable hydrophilic polymers include: hydroxypropylmethylcellulose; hydroxypropylcellulose; methylcellulose; hydroxymethylcellulose; hydroxyethylcellulose; hydroxypropylcellulose, which can be used alone or in combination; carboxymethylcellulose and the sodium salt thereof, which can be used alone or in combination; and other hydrocolloids, such as acacia and guar gum (column 2, lines 57-64). As discussed during the interview, Sangekar et al do not teach a combination of HEC and HPMC as presently claimed. At best, Sangekar et al may suggest the equivalence of these various swellable hydrophilic polymers in their compositions.

The Examiner has relied on Zhang et al as disclosing a combination of HEC and HPMC. Zhang et al disclose sustained release formulations containing three different types of polymers, namely a pH dependent gelling polymer, an enteric polymer and a pH

independent gelling polymer. Zhang et al disclose at column 2, beginning at line 6, that the pH independent gelling polymer may be, for example, a hydroxyl propyl methyl cellulose, a hydroxyl propyl ethyl cellulose, a hydroxyl propyl cellulose, a hydroxyl ethyl cellulose, a methyl cellulose, a xantham gum or a polyethylene oxide. Each of the exemplary compositions of Zhang et al at column 3 containing the active verapamil HCl, at column 4 containing the active pentoxyfilline, and at column 4 containing the active nifedipine contains one pH independent gelling polymer. In claim 2, Zhang et al recite that the pH independent gelling polymer comprises at least one of a hydroxyl propyl methyl cellulose, a hydroxyl propyl ethyl cellulose, a hydroxyl propyl cellulose, a hydroxyl ethyl cellulose, a methyl cellulose, xantham gums, or a polyethylene oxide, although the Zhang et al specification provides no teaching of a combination of pH independent gelling polymers. At best, Zhang et al, like Sangekar et al, teach the equivalence of the listed pH independent gelling polymers in their compositions.

Applicants have discovered however that HEC and HPMC are not equivalent for use in sustained release compositions and their use in combination provides improvements over their individual use. As discussed, the first Declaration Under 37 C.F.R. 1.132 previously submitted in this application, particularly paragraph 3 and Table 2, describes the preparation of three compositions respectively containing 15% HPMC, 15% EC and 15% HEC. Table 2 set forth in the Declaration indicates that the dissolution rates of the three compositions were significantly different from one another, whereby the availability of active during dissolution of the respective compositions was significantly different. These results demonstrate that, contrary to teachings of Sangekar et al and Zhang et al, HPMC, HEC and EC are not equivalent in controlled release compositions.

The Second Declaration Under 37 C.F.R. 1.132 describes the preparation and study of three compositions containing a model drug and, respectively, (a) 10% HPMC in combination with 10% HEC, according to the invention, (b) 20% HPMC (comparative), and (c) 20% HEC (comparative). The dissolution rates of these three compositions are set forth at pages 2 and 3 of the Declaration. As is apparent, these results show differences in rate of dissolution when the same drug is formulated with (a) a combination of 10% HEC and 10% HPMC, versus (b) 20% HEC, or (c) 20% HPMC. For example, at one hour, 39.05% of the model drug was released from composition (a) containing the HEC/HPMC combination, while only 28.83% of the model drug was released from the composition (b) containing only HPMC, yet 98.15% was released from composition (c) containing only HEC. These differences in dissolution rates are significant, especially with high potency drugs where both immediate and delayed release are necessary. Particularly, composition (a) according to the invention provides improved early dosing over composition (b) and improved delayed dosing over composition (c). The improved model drug release profile exhibited by composition (a) as compared with compositions (b) and (c) is neither taught nor suggested by either Sangekar et al or Zhang et al, as these references do not teach or suggest any of HPMC, HEC or combinations of HPMC and HEC as having any differences in drug release profiles.

Thus, these Declarations show unexpected results provided by the presently claimed compositions as compared with the teachings of Sangekar et al and Zhang et al which, at best, teach equivalence of various polymers in their disclosed compositions. A prima facie case of obviousness can be rebutted by evidence of unexpected results, *In re Davis*, 177 U.S.P.Q. 381 (CCPA 1973). When an Applicant demonstrates substantial improved results and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary, *In re Soni*, 34 U.S.P.Q. 2d 1684 (Fed. Cir. 1995). The showings

set forth in the Declarations show unexpected improvement and therefore rebut any prima facie case of obviousness established by the Examiner based on Sangekar et al and Zhang et al.

The Examiner has cited Stupak et al as disclosing the claimed excipients. However, as Applicants find no teaching or suggestion by Stupak et al of controlled release pharmaceutical compositions providing a combination of HPMC and HEC as presently claimed, or relating to the improvements provided by such a combination in a controlled release pharmaceutical composition, Stupak et al do not resolve the deficiencies of Sangekar el al and Zhang et al.

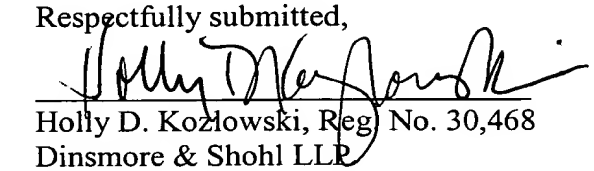
Finally, the Examiner asserted in the Official Action that the combination of cited prior art permits one of ordinary skill in the art to design an experiment to obtain a biphasic controlled release of drug and thereby expect the results presented in the Declaration because a drug release rate can be adjusted by changing the amount of one or more of the component polymers. Applicants submit that the Examiner's statement is not relevant to a determination of patentability under 35 U.S.C. §103. That is, to deny patentability of the present claims under 35 U.S.C. §103, the Examiner must demonstrate the differences between the subject matter sought to be patented and the prior art are such that the subject matter as whole would have been obvious at the time the invention was made to a person having ordinary skill in the art, 35 U.S.C. §103(a). The Examiner's assertions do not meet this requisite burden as none of the Sangekar et al, Zhang et al and Stupak et al teach or suggest the combination of HPMC and HEC in a controlled release formulation as presently claimed, or the improvements in a controlled release pharmaceutical composition provided by such a combination.

It is therefore submitted that claims 1-3 and 5-35 are nonobvious over and patentably distinguishable from the combination of Sangekar et al, Zhang et al and Stupak et al, whereby

the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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